R-wave Amplitude in Lead II of an Electrocardiograph Correlates with Central Hypovolemia in Human Beings

John G. McManus, MD, MCR, Victor A. Convertino, PhD, William H. Cooke, PhD, David A. Ludwig, PhD, John B. Holcomb, MD

Abstract

Objectives: Previous animal and human experiments have suggested that reduction in central blood volume either increases or decreases the amplitude of R waves in various electrocardiograph (ECG) leads depending on underlying pathophysiology. In this investigation, we used graded central hypovolemia in adult volunteer subjects to test the hypothesis that moderate reductions in central blood volume increases R-wave amplitude in lead II of an ECG.

Methods: A four-lead ECG tracing, heart rate (HR), estimated stroke volume (SV), systolic blood pressure, diastolic blood pressure, and mean arterial pressure were measured during baseline supine rest and during progressive reductions of central blood volume to an estimated volume loss of >1,000 mL with application of lower-body negative pressure (LBNP) in 13 healthy human volunteer subjects.

Results: Lower-body negative pressure resulted in a significant progressive reduction in central blood volume, as indicated by a maximal decrease of 65% in SV and maximal elevation of 56% in HR from baseline to −60 mm Hg LBNP. R-wave amplitude increased ($p < 0.0001$) linearly with progressive LBNP. The amalgamated correlation (R^2) between average stroke volume and average R-wave amplitude at each LBNP stage was −0.989.

Conclusions: These results support our hypothesis that reduction of central blood volume in human beings is associated with increased R-wave amplitude in lead II of an ECG.

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Keywords: hemorrhage, LBNP, R-wave amplitude, trauma

For soldiers and civilians of the United States, uncontrollable hemorrhage accounts for almost 50% of combat fatalities and for up to 80% of civilian trauma fatalities.[1,2] Because hemorrhage continues to be a leading cause of death, development of new approaches for early detection of blood loss in austere environments has continued to be a research priority. Several triage criteria and tools have been advocated to determine injury severity, mode of transport, priorities of treatment, and patient destination for the triage of trauma patients.[3–15] However, most existing triage tools currently use the patients' vital-signs data, on the assumption that these measurements are readily obtainable at the site of injury and therefore provide a snapshot of patient stability. Such an assumption is problematic because the physiology of the trauma patient with severe hemorrhage is dynamic. The absence of frequent physiological measurements that are available in the out-of-hospital setting necessitates that out-of-hospital providers make rapid decisions about priority of care, application of interventions, and transport destinations on the basis of isolated data points (e.g., arterial pressure, heart rate [HR], and respiratory rate) without the benefit of observing dynamic trends inherent to trauma physiology. Thus, the current process and practice of out-of-hospital trauma care may be significantly improved by providing appropriate continuous physiological observations that are based on signals that

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may provide the best early indicators of blood volume loss and impending circulatory collapse.

During early volume loss, a series of reflex cardiovascular and neurohormonal mechanisms maintain normal arterial pressures with only mild tachycardia. The baroreceptor reflexes, chemoreceptor reflexes, and cerebral ischemia initiate strong sympathetic responses that result in intense vasoconstriction and help defend against severe hypotension. Therefore, use of standard vital signs may not truly reflect early volume loss. However, a direct linear relationship between body-surface voltage and intracardiac volume has been reported.[16–20] If R-wave amplitude faithfully represents cardiac volume independent of reflex responses, then continuous electrocardiograph (ECG) R-wave amplitude evaluations may serve as an improved early marker of central blood-volume reductions.

Department of Defense research projects are focusing on sensors to be worn by soldiers in austere conditions for possible use in remote triage and diagnostic medical decision making. Because it is likely that ECG leads, particularly leads I, II, or III, will be worn in the future by soldiers on the battlefield, changes of R-wave amplitude may help to predict severity of hemorrhage and facilitate early decisions regarding diagnosis, treatment, and evacuation of combat casualties. In the present investigation, we compared R-wave amplitude, HR, arterial pressures, and stroke volume (SV) at rest and during graded exposure to lower-body negative pressure (LBNP) to test the hypothesis that R-wave amplitude in ECG signals is related inversely to central blood volume in human beings who are exposed to a noninvasive model of central hypovolemia.

METHODS

Study Design

This was a prospective, unblinded clinical study performed at the U.S. Army Institute of Surgical Research. Approval was obtained from the local institutional review board at Brooke Army Medical Center, and informed consent was obtained from all participants.

Study Setting and Population

Subjects for this experiment were 13 healthy, normotensive men who were aged 27–52 years and representative of the general military population. All subjects were nonsmokers with no history of autonomic dysfunction and underwent a health history and physical exam by a physician. Individuals were excluded from the study if they were taking prescription medications regularly or if they had a history of hypertension or any chronic cardiopulmonary medical condition. Subjects abstained from medications, caffeine, exercise, and alcohol for at least 48 hours before the experiment.

Study Protocol

Subjects were placed in supine position and underwent an LBNP protocol consisting of a 12-minute baseline period, followed by exposure to −15, −30, −45, and −60 mm Hg decompression for 12 minutes each and then by a return to baseline (0 mm Hg). LBNP was used as a method to induce central hypovolemia and subsequent hemodynamic responses that were similar to those measured during a steady-state hemorrhage.[16,21,22] LBNP exposure to −60 mm Hg has been shown to induce hemodynamic responses associated with blood loss greater than 1,000 mL.[16,23–25] A human research volunteer in the LBNP chamber is shown in Figure 1.

The initial 2 minutes of each 12-minute data collection period was used to allow the subject to reach a steady-state status without data collection.[21] For 3 minutes during each stage, subjects controlled their breathing rate at a strict 15 breaths per minute (0.25 Hz) for the purpose of recording ECG and assessing HR variability. Results of HR variability have been reported elsewhere.[26,27] Breathing at 15 breaths per minute may be faster than subjects' normal, unpaced breathing rate, but our purpose was to

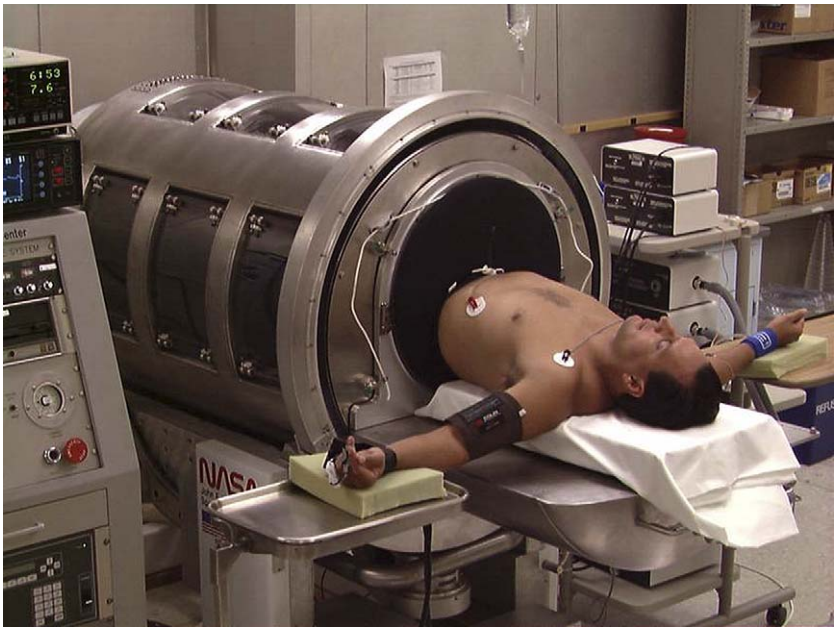

Figure 1. Subject undergoing experiment in the lower-body negative pressure chamber.

ensure that oscillations of R-R intervals occurring at the respiratory frequency were not confounded inappropriately by harmonics of low frequency rhythms occurring around 0.1 Hz. Measurements during baseline and each LBNP level included HR, SV, and arterial blood pressures. Subjects were instructed not to contract their leg muscles during LBNP. Premature test termination was based on occurrence of any one or a combination of the following: 1) onset of symptoms of cardiovascular collapse, such as a fall in systolic blood pressure (sBP) of more than 15 mm Hg or a fall in HR of more than 15 beats per minute between adjacent 1-minute measurements; 2) progressive fall in sBP below 80 mm Hg; and 3) subject request as a result of presyncopal symptoms such as nausea, dizziness, or lightheadedness. To ensure subject safety, a medical monitor (who was certified in Advanced Cardiac Life Support) was present during the entire experiment and throughout the recovery period.

Measurements

Continuous HR was measured with a Gould Instrument System (Biotach Amp Model 6600, Valley View, OH) from a four-lead ECG with lead II configuration. Systolic blood pressure and diastolic blood pressure (dBP) measurements were performed at the 8th minute of each LBNP stage with a Colin automated sphygmomanometer (STBP-780, San Antonio, TX). Mean arterial pressure (MAP) was calculated by dividing the sum of sBP and twice dBP by three.

Stroke volume was measured noninvasively by using thoracic electrical bioimpedance. Thoracic impedance was measured with four circumferential electrodes, two placed around the base of the neck and two placed around the thorax at the level of and distal to the xiphoid process. A bioelectric impedance cardiograph unit (HIC-2000; Bio-impedance Technology, Inc., Chapel Hill, NC) was used to introduce a constant current of 4 mA at 100-KHz frequency across the outer electrodes and to detect changes in electrical impedance with each pulse beat across the inner pairs of electrodes.[28] The analog signal of the ECG waveform, baseline thoracic impedance (Z_0), and the change in impedance over time (dZ/dt) were converted to a digital signal for analysis by using Lab View (National Instruments, Austin, TX) software. The following algorithm[28] was used to estimate SV from the ECG and impedance:

$$SV = \frac{\rho L^2 T (dZ/dt)_{min}}{Z_0^2},$$

where ρ was the average electrical resistivity of blood at 100 KHz (150 ohm-cm), L was the mean distance between the two inner electrodes in centimeters, and T was the ventricular ejection time in seconds, as measured from the dZ/dt and ECG waveforms. An example of measurements obtained from analog tracings for this calculation is shown for one cardiac cycle in Figure 2.

The R wave of the ECG was taken as a landmark for averaging dZ/dt waveforms over 10 cardiac cycles that were recorded at the beginning of minutes 2, 8, and 10 of each baseline and LBNP level. SV for minutes 2, 8, and 10 were determined as the average SV from the 10 cardiac cycles, and average SV at baseline and each level of LBNP was calculated as the average of the SV measured at 2, 8, and 10 minutes. Estimates of SV by using thoracic impedance have been reported to have correlation coefficients of 0.70 to 0.93 in comparison with thermodilution techniques.[29]

Data were sampled at 500 Hz and were recorded directly to computer with commercial hardware and software (WINDAQ; Dataq instruments, Akron, OH) and then were imported into data analysis software (WinCPRS; Absolute Aliens, Turku, Finland). R waves generated in lead II from the four-lead ECG signal were detected and marked at their occurrence in time. R-wave amplitude was determined from the mean of a sample of 20 consecutive beats at baseline and during −15, −30, −45, and −60 mm Hg LBNP. Each R wave was measured from the base of the R wave to the peak of the R wave to eliminate any variance in baseline drift. An example of ECG tracing with measurements comparing R-wave amplitude at baseline rest (0 mm Hg LBNP) and 60 mm Hg LBNP from one subject is presented in Figure 3.

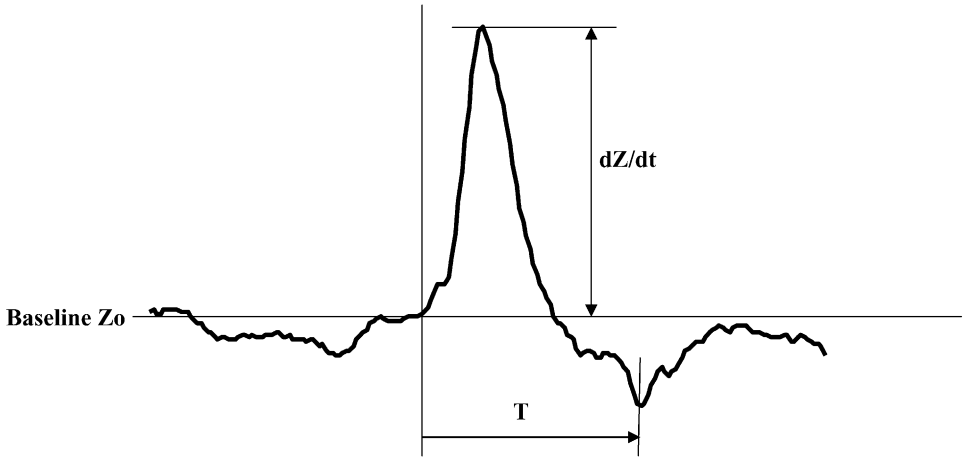

Figure 2. Example of an analog signal tracing of the thoracic electrical bioimpedance cardiogram waveform used to determine baseline thoracic impedance (Z_0), the change in impedance over time (dZ/dt), and the ventricular ejection time (T) and to calculate stroke volume.

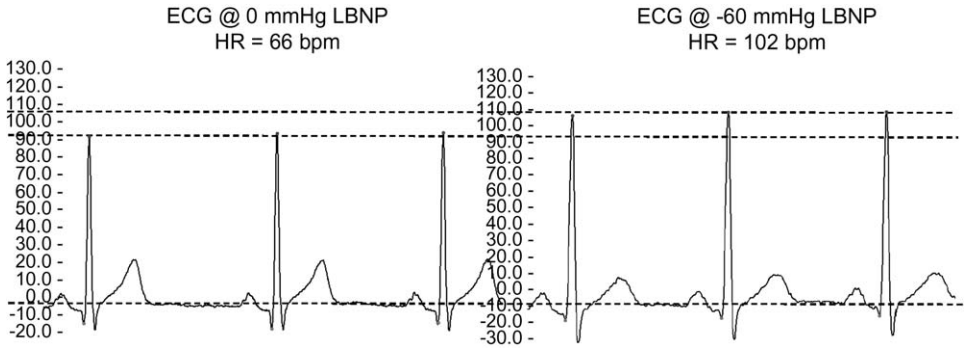

Figure 3. Example of analog signal tracings of the electrocardiogram (ECG) waveform recorded from a single subject at baseline rest (0 mm Hg lower-body negative pressure [LBNP]) and at 60 mm Hg LBNP to determine R-wave amplitude. HR = heart rate.

Data Analysis

LBNP level means calculated for HR, sBP, dBP, MAP, SV, and R wave were compared with one-way, repeated-measures analysis of variance (ANOVA). Within the framework of the repeated-measures ANOVA, orthogonal polynomial subdivision (trend analysis) was used to define and statistically test the shape of the dose response across LBNP levels.[30] Exact p-values derived from the polynomial subdivision within the ANOVA reflect the probability of observing a similar or greater effect (i.e., trend in the dose response), given the assumption that LBNP has no effect on the dependent variables (i.e., flat dose response). Data are presented as means ± SEM. The SEs given in the figures and in this article are raw SEs. They are not adjusted for subject-to-subject variability and therefore do not directly reflect the results of the repeated-measures ANOVA.

RESULTS

The means across LBNP levels for all six dependent variables are given graphically in Figure 4. Progressive LBNP resulted in a linear reduction (recovery LBNP not considered) in central blood volume, as indicated by a proportional decrease in SV from 125 ± 9 mL at baseline to 43 ± 6 mL at 60 mm Hg LBNP [$F_{\text{linear trend}}(1,12) = 82.5$, $p < 0.0001$]. A similar linear decrease was seen in sBP from 129 ± 3 mm Hg at baseline to 111 ± 6 mm Hg at

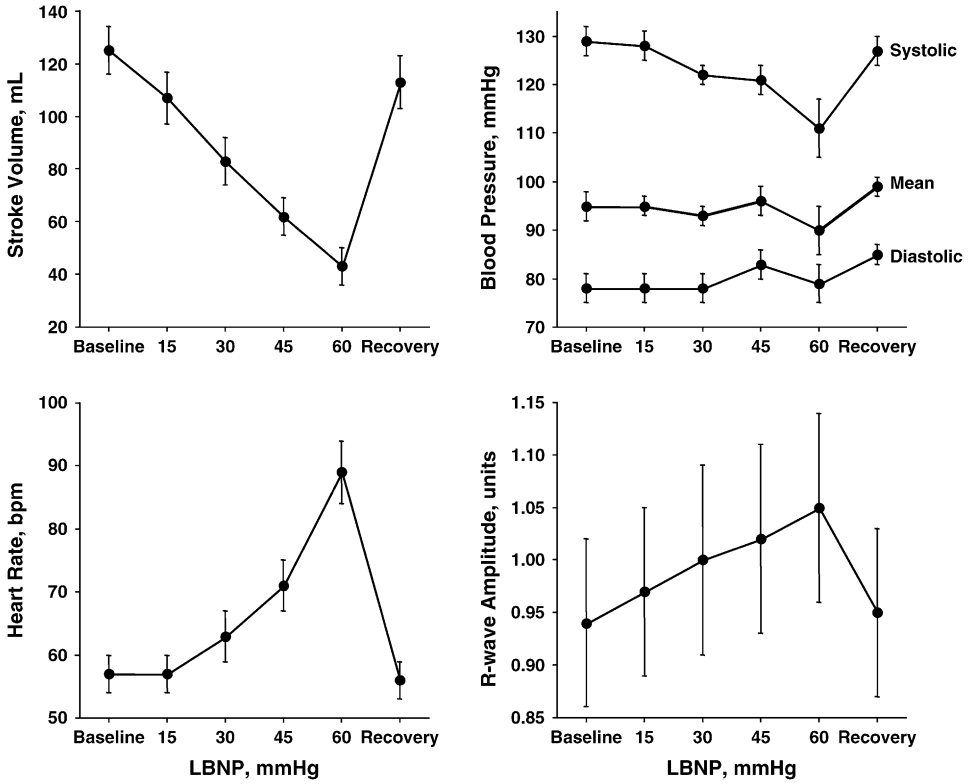

Figure 4. Responses of stroke volume, heart rate, blood pressures, and R-wave amplitude during progressive levels of lower-body negative pressure (LBNP) and after recovery from LBNP. Error bars shown are SEMs.

60 mm Hg LBNP [$F_{\text{linear trend}}(1,12) = 13.1$, $p = 0.0035$]. The trend for HR was curvilinear, increasing from 57.4 ± 3 beats/min at baseline to 88.5 ± 5 beats/min at 60 mm Hg LBNP [$F_{\text{curvilinear trend}}(1,12) = 61.0$, $p < 0.0001$]. There were no statistical differences in dBP or MAP [$F_{\text{any trend}}(4,48) \leq 1.10$, $p \geq 0.3679$] across LBNP levels. R-wave amplitude increased linearly with progressive LBNP [$F_{\text{linear trend}}(1,12) = 21.8$, $p = 0.0005$]. In addition, the R wave raised from 0.939 ± 0.160 amplitude units at baseline to 1.05 ± 0.176 amplitude units at 60 mm Hg LBNP. Specific to the research hypothesis, during progressive LBNP, R-wave amplitude increased as stroke volume decreased. Scatter plots of this relationship for individual subjects (recovery LBNP included) are presented in Figure 5. The amalgamated correlation (i.e., R^2 between the average values for all 13 subjects at each LBNP level) between stroke volume and R-wave amplitude was 0.989 (Figure 6).

DISCUSSION

In the present investigation, we measured the height of R waves during baseline rest and at graded levels of LBNP to test the hypothesis that R-wave amplitude of an ECG is associated with central blood volume (the Brody effect).[31] A significant central hypovolemia was verified by an average 65% reduction in stroke volume and a 56% compensatory tachycardia. The major finding of the present study was that R-wave amplitude obtained from a lead II ECG was related inversely to central blood volume when otherwise healthy human subjects were introduced to a model of progressive central hypovolemia (i.e.,

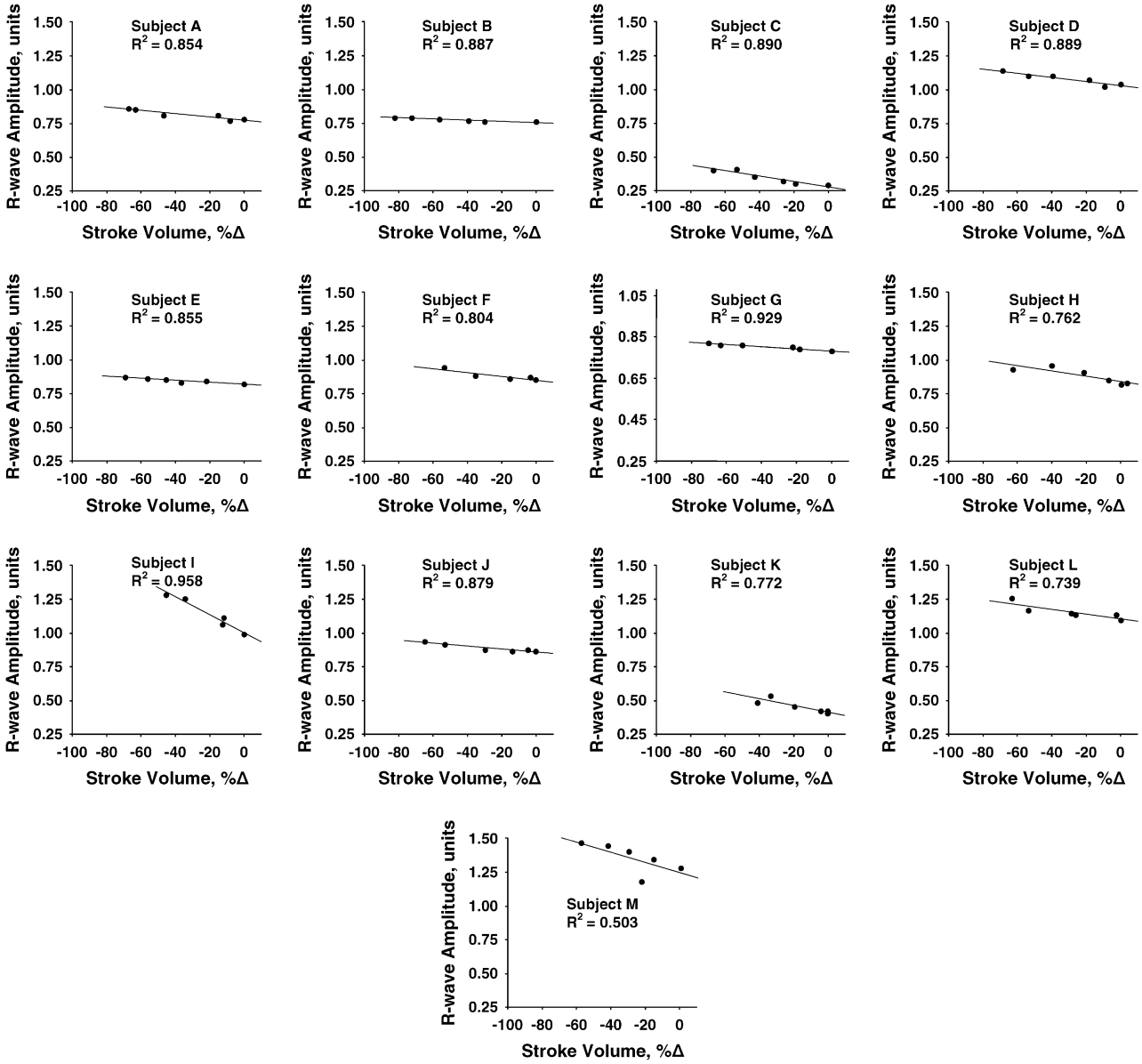

Figure 5. Individual relationships and correlation coefficients (R^2) between stroke volume and R-wave amplitude obtained from 13 subjects.

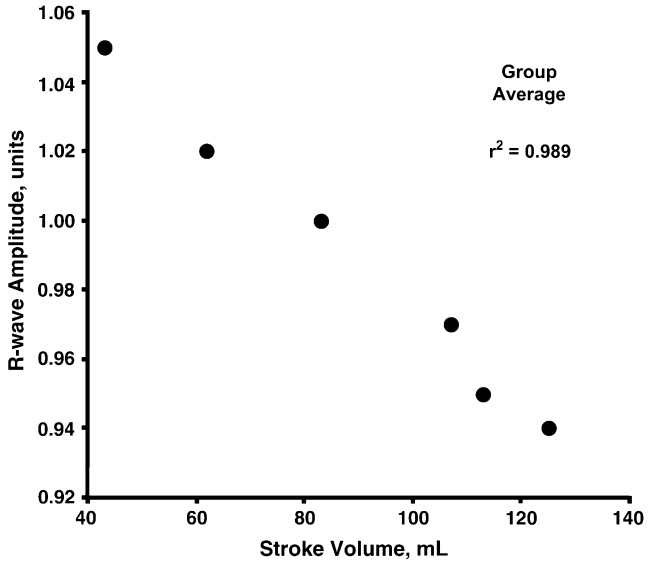

Figure 6. Average relationship for whole group between stroke volume and average R-wave amplitude.

LBNP). Further, our data indicate that the change in R-wave amplitude occurred at an earlier time of central blood volume loss than measurements of arterial blood pressure. In this regard, these results are the first to demonstrate in human beings that measurements of R-wave amplitude may improve the ability to predict severity of hemorrhage and facilitate early decisions regarding diagnosis, treatment, and evacuation of combat casualties.

In 1956, Brody[31] published a theoretical analysis that proposed a direct relationship between QRS complex voltage and ventricular blood volume, a relationship that later became known as the Brody Effect. Brody's theory was that blood is an excellent conductor of electricity and that a decrease in blood volume would reduce the myocardial dipoles that serve as the source of surface potential for the ECG.[29] The Brody Effect has been supported by both animal[32–35] and human[36–38] experiments. However, other investigations have reported mixed results, with R-wave or QRS amplitude having an inverse[16–20] or no relationship[39,40] with a reduction in central blood volume. The reasons for these varying results are unclear but may be related to the use of different technical methods such as hemodialysis, ischemia, cardiac pacing, Valsalva maneuvers, and stress testing, which may have confounded the interpretation of results.[38–40] We used a noninvasive model of systematically controlled progressive central blood-volume reduction with continuous measures of R-wave amplitude, stroke volume, and blood pressures in an effort to control the impacts of extraneous factors on the R-wave response. With this model, we found that our results did not support the relationship described by the Brody Effect.

The inverse relationship between body-surface voltage and cardiac volume has been described in previous studies.[16–20] In the study by Ishikawa et al.,[18] the investigators postulated that decrease in cardiac volume resulted in a decrease of the surface area of the inner wall of the left ventricle, which reduced internal current flow. This reduction in current flow short-circuits the internal electric field, resulting in an increase of the body-surface voltage potential. Plonsey and Barr[41] represented this relationship as the following equation:

$$V_{ab} = \blacktriangledown\Phi \times H,$$

where V_{ab} represents the voltage between two leads, $\blacktriangledown\Phi$ represents the lead vector field, and H is the net dipole source activity from the heart vector. Because Φ is inversely proportional to unit current, a decrease in current (which increases lead field) would result in an increase in voltage measured by the leads. Our results are consistent with those from these investigations, which provide evidence of an inverse relationship between R-wave amplitude and central blood volume. Furthermore, our hypothesis is supported by the fact that R-wave amplitudes returned to baseline in all subjects once central volume was restored.

Although use of ECG waveforms as a predictor of mortality and blood loss in trauma patients is not a new concept, ours is the first study to assess alterations in R-wave amplitude during a controlled reduction in central blood volume. Other nonstandard applications of the ECG waveform also are being investigated for trauma care. For example, analysis of heart rate variability has shown promise as a tool for predicting mortality in out-of-hospital trauma patients.[42,43] HR variability analysis has also been shown to decrease predictably and as a linear function of progressive reductions of central blood volume.[44] The R-wave amplitude represents another approach to deriving hemodynamic information from the ECG for use as an early predictor of volume loss.

LIMITATIONS

Our results should be considered in light of at least five limitations. First, our laboratory model of progressive central hypovolemia provides a unique opportunity to collect continuous data on changes in ECG waveforms, but we recognize that cardiovascular responses to experimentally induced central hypovolemia may be different when compared with responses to actual severe hemorrhage. Although LBNP induces fluid redistribution from the upper to lower body rather than actual blood loss, previous experiments have shown that many of the physiological responses to LBNP are similar to those of actual volume loss up to as much as 1,000 mL.[23–25] It is noteworthy that the limitation that LBNP is not hemorrhage also may be a benefit. By using this model, we were able to assess the relationship between R-wave amplitude that was measured from continuous ECG recordings and reduced central volume without confounding factors such as tissue injury and pain stimuli that might have affected autonomic nerve and cardiac electrical potentials. Therefore, our results may be the first to reflect strictly on the relationship between reduced central blood volume and ECG amplitudes in human subjects. Second, measurements of R-wave amplitude were limited to a lead II configuration of the ECG. We cannot dismiss the possibility that R-wave changes may be different during reductions in central blood volume in other leads. Of note, the lead II configuration from a four-lead ECG (not 12-lead ECG) is the current standard in the majority of civilian and military out-of-hospital trauma patients. Third, the use of normal, healthy subjects could have biased the results. In fact, one subject was a runner who clearly was

aerobically fit, with a resting heart rate of 33 beats per minute. In most previous studies, subjects had underlying pathophysiology that may have influenced potentiated amplitude changes with volume loss. Fourth, measuring stroke volume with bioimpedance is an indirect method. Although we observed the expected progressive, linear reductions of SV with LBNP, we stress that the actual volume of fluid displaced was not determined. Finally, there is substantial subject-to-subject variability in R-wave amplitude that limits the use of average population changes for prediction of central blood volume loss. However, it is clear from our data that within any given individual, changes in central blood volume are tracked by changes in R-wave amplitude.

CONCLUSIONS

R-wave amplitude obtained from a lead II ECG is related inversely to central blood volume in healthy human subjects during progressive central hypovolemia (i.e., LBNP). Changes of R-wave amplitudes occur before changes of arterial pressures, and, therefore, amplitude monitoring may allow for early identification of blood loss as a result of hemorrhage. ECG monitors that may in the future support analysis of R-wave amplitude could improve the ability to predict severity of hemorrhage and to facilitate early decisions regarding diagnosis, treatment, and evacuation of combat casualties.

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